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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/529,923
Filing Date: August 29, 2005
Appellant(s): SAVIO ET AL.

James F. Harrington
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 3/11/2009 appealing from the Office action mailed 10/16/2008.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal.

The appellant's statement of the grounds of rejection to be reviewed on appeal is substantially correct. The changes are as follows: Appellants have inadvertently listed Grabstein *et al* as "WO 95/2772". The correct citation for Grabstein *et al* is "WO 95/27722".

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Grabstein *et al* (WO 95/27722)

Brewer J.M. *et al.* Aluminium Hydroxide Adjuvant Initiates Strong Antigen-Specific Th2 Responses in the Absence of IL-4- or IL-13-Mediated Signaling. Journal of Immunology, 1999, Vol. 164, pp. 6448-6454.

Gonzalez S, *et al.* P64k Meningococcal Protein as Immunological Carrier for Weak Immunogens. Scandanavian Journal of Immunology. 2000, Vol. 52, pp. 113-116.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 22-23 rejected under 35 U.S.C. 103(a) as being unpatentable over Grabstein *et al* (WO 95/27722) in view of Gonzalez *et al* (*Scand. J. Immunol.*, 2002, Vol. 52, p. 113-116), and further in view of Brewer *et al* (*J. Immunol.*, 1999, Vol. 163, p. 6448-6454).

The claims of the present invention are drawn to a method for generating a neutralizing antibody response against autologous interleukin (IL)-15 in a primate, wherein said method comprises

administering to said primate a composition comprising human IL-15 and aluminum hydroxide, wherein the IL-15 is an antigen and wherein said IL-15 antigen generates neutralizing self-antibodies against IL-15. Dependent claim 23 is further drawn to this method, wherein the IL-15 antigen is coupled to a carrier protein, and wherein the carrier protein is P64k protein.

Grabstein *et al* discloses cloning and characterization of several IL-15 polypeptides, including human IL-15 (Grabstein *et al*, p. 2, lines 29-39). Grabstein *et al* teaches that IL-15 is a T-cell stimulatory cytokine which stimulates proliferation of T cells, including inducing proliferation and/or differentiation of both precursor and mature T cells (Grabstein *et al*, p. 4, lines 16-29). Grabstein *et al* also teaches pharmaceutical compositions comprising IL-15, and administration of IL-15 to subjects (Grabstein *et al*, p. 15, line 25 - p. 16, line 2). Grabstein *et al* does not teach administration of a composition comprising human IL-15 and aluminum hydroxide for the purpose of generating a neutralizing antibody response against autologous IL-15.

However, Brewer *et al* discloses that the aluminium hydroxide (alum) is useful as a vaccine adjuvant because the use of alum/aluminium hydroxide induces antigen specific antibodies when administered with an antigen, and in particular, is useful for generating neutralizing antibodies (see Brewer *et al*, p. 6448, 1st column, 1st paragraph). Brewer *et al* does not teach the use of aluminum hydroxide in a composition with human IL-15.

Gonzalez *et al* shows that the meningococcal protein P64k functions as an effective carrier protein when conjugated to weakly immunogenic proteins. Specifically, Gonzalez *et al* discloses that conjugation of P64k to other proteins induced higher antibody titers upon immunization compared to immunization with proteins which were not conjugated to P64k (Gonzalez *et al*, abstract, and page 114-115, and Figures 1-3 which show higher antibody levels generated by immunization with proteins conjugated to P64kcompared to unconjugated proteins). Gonzalez *et al* also teaches that antigens conjugated to P64k can be used in conjunction with the adjuvant aluminium hydroxide (Gonzalez *et al*, p.

115, 2nd column, lines 15-17 of the first "Discussion" paragraph). Gonzalez et al dies not teach conjugation or coupling of P64k to human IL-15 for the purpose of generating neutralizing antibodies.

However, it would have been *prima facie* obvious to one of ordinary skill in the art, at the time the instant invention was conceived, to administer a composition comprising human IL-15 and aluminium hydroxide to a primate, wherein the IL-15 may or may not be coupled to P64k protein, for the purpose of generating antibodies specific for IL-15. The motivation to do so is provided by the disclosure of Grabstein *et al*, which teaches IL-15 polypeptides and shows that IL-15 exerts an important immunological function, namely that of stimulating proliferation or differentiation of both precursor and mature T cells. Therefore, a person of ordinary skill in the art, at the time the instant invention was filed, would have be motivated to further study the biological functions of IL-15 in both normal and pathological settings. Grabstein *et al* discloses the use of antibodies for the study of the biological properties of another cytokine, IL-2, in which anti-IL-2 antibodies were used to reveal differences between IL-2 and IL-15 (Grabstein *et al*, p. 4, lines 29-31). For these reasons, a person of ordinary skill in the art would have been motivated to administer a composition comprising IL-15 to a primate for the purpose of generating antibodies which would be useful in the isolation and/or characterization of the biological properties of IL-15.

The motivation to administer a composition comprising IL-15 and aluminium hydroxide is provided by Brewer *et al*, which shows that administration of alum/aluminium hydroxide in conjunction with an administered antigen increases antigen-specific antibody production and also produces neutralizing antibodies. Motivation to couple IL-15 to P64k is similarly provided by Gonzalez *et al*, which would show a person of ordinary skill in the art that the antibody response to IL-15 could be increased by coupling to P64k.

Therefore, a person of ordinary skill in the art would be motivated by Grabstein *et al* to produce antibodies specific for IL-15 for use in further characterization and study of IL-15, and would also be

motivated, via Brewer *et al* and Gonzalez *et al*, to administer the IL-15 in a composition comprising aluminium hydroxide, or administer IL-15 coupled to P64k protein, because the person of ordinary skill would know that these methods would result in the production of high levels of antibodies specific for IL-15, wherein said antibodies would be useful for further study of IL-15.

(10) Response to Argument

On page 6, 3rd full paragraph, of the Appeal Brief, the Appellants argue that claim 22 relates to a method for generating a neutralizing antibody response against autologous IL-15. Specifically, claim 22 states in the final "wherein" clause that the "IL-15 antigen generates neutralizing self-antibodies against IL-15." Accordingly, the Appellants are not claiming the creation of any "neutralizing antibodies for the study of IL-15 biological activities and properties", but are rather claiming a method in which the administration of human IL-15 generates neutralizing self-antibodies against IL-15. The Appellants argue that none of the cited references disclose or suggest this claimed method.

On page 7, 1st and 2nd paragraphs, of the Appeal Brief, the Appellants argue that Grabstein *et al* teaches that T cells are a class of immune effector cells which can be split into two general classes: cytotoxic T cells and T helper cells. Cytotoxic T cells are activated when they interact with an antigen-class I MHC complex on the surface of an altered self-cell in the presence of appropriate cytokines, while T helper cells are activated by the recognition of an antigen-class II MHC complex on an antigen-presenting cell. After activation, the T helper cell divides and gives rise to a clone of effector cells which secret various cytokine, which play a central role in the activation of B cells, T cells, and other cells that participate in the immune response. The Appellants also note that Grabstein *et al* discloses that six T-cell growth factors, IL-2, -4, -7, -9, -12, and -10, had been previously identified, and that Grabstein *et al* discloses that they identified a novel T-cell growth factor, referred to as IL-15. Grabstein et al shows that IL-15 promotes stimulation of CTLL-2 proliferation, and concludes on page 24 that "one of ordinary skill

in the art would expect IL-15 to stimulate the activity of CTL, LAK, and NK cells and *expand* the population of T cells that can destroy tumor cells and viral-infected cells". [emphasis added]. However, in contrast, the Appellants argue on page 7, 3rd paragraph through page 8, 1st paragraph of the Appeal Brief, that the claimed invention relates to a method of generating a neutralizing antibody response against autologous IL-15 in a primate. Instead of stimulating T lymphocyte proliferation as disclosed in Grabstein *et al*, the claimed neutralizing response would inhibit the activity of IL-15 as a cytokine as disclosed by Grabstein *et al*. Thus, the claimed method results in inhibition of IL-15 induced CTLL-2 proliferation, as evidenced by Example 3 of the instant application, whereas Grabstein *et al* demonstrate stimulation of CTLL-2 proliferation using IL-15.

For these reasons, the Appellants argue that Grabstein *et al* does not provide motivation for the presently claimed invention, but instead teaches away from administering IL-15 to generate neutralizing self-antibodies against IL-15.

Appellants' arguments have been fully considered but are not found persuasive for the following reasons. In regards to Appellants' arguments that the claimed method is not directed towards generation of antibodies for the study of biological activities and properties of IL-15 but are instead drawn to a method of generating neutralizing self-antibodies against autologous IL-15, it is noted that administration of IL-15 with aluminium hydroxide, with or without coupling of IL-15 to P64k protein, as suggested by the combination of Grabstein *et al*, Brewer *et al*, and Gonzalez *et al* for the production of antibodies useful for studying biological properties of IL-15, would be expected to produce antibodies specific for autologous IL-15, and wherein these antibodies are neutralizing antibodies. Appellants' own specification, in Examples 3 and 4, as well as the arguments on page 7, 3rd paragraph of the Appeal Brief, show that administration of IL-15 with aluminium hydroxide, or IL-15 coupled to P64k protein, results in neutralizing antibodies against autologous IL-15. Therefore, although the combination of Grabstein *et al*,

Brewer *et al*, and Gonzalez *et al* provide motivation to practice a method of administering IL-15 with aluminium hydroxide and/or P64k for reasons that differ from the Appellants' motivation, namely for the production of antibodies useful for studying IL-15 vs. Appellants desire to inhibit IL-15 in diseases in which IL-15 is over-expressed (see Appeal Brief, paragraph spanning pages 5-6), the method steps and reagents of both methods would be identical. Therefore, in the absence of evidence to the contrary, a method of administering IL-15 and aluminium hydroxide, wherein the IL-15 may or may not be coupled to P64k protein, for the purpose of generating antibodies for studying IL-15 biological properties, would *inherently* produce neutralizing antibodies against autologous IL-15.

Regarding Appellants' arguments that Grabstein *et al* teaches away from the claimed invention, it is noted that Grabstein *et al* provides adequate motivation to produce antibodies specific for IL-15, as set forth above. The showing in Grabstein *et al* of IL-15 stimulated CTLL-2 cell proliferation *in vitro* merely shows a biological role of IL-15. Thus, Appellants are arguing a teaching away based on two different biological properties of IL-15 (stimulation of T cell proliferation vs the ability to behave as an antigen) in vastly different biological systems (*in vitro* proliferation vs *in vivo* generation of an antibody response). While Grabstein *et al* teaches stimulation of T cell proliferation by IL-15, there is noting in Grabstein *et al* which would indicate that it would not be a suitable antigen for the purpose of producing IL-15 specific antibodies.

For these reasons and those discussed above, a person of ordinary skill in the art, at the time the instant invention was conceived, would have been motivated by the combination of Grabstein *et al*, Brewer *et al*, and Gonzalez *et al* to administer IL-15 and aluminium hydroxide, including IL-15 coupled to P64k protein, to a primate for the purpose of generating antibodies for use in the further study and characterization of IL-15. Because the obvious method would necessarily involve method steps and reagents which are identical to the claimed method, this obvious method would *inherently* produce

neutralizing self-antibodies specific for autologous IL-15 that meet the limitations of the presently claimed invention.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Bruce D. Hissong /

Examiner, Art Unit 1646

Conferees:

/Gary B. Nickol /

Supervisory Patent Examiner, Art Unit 1646

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